Remarks

Claims 10-20 are pending in the subject application. By this Amendment, Applicants have amended claims 10 and 13 and added new claims 21-26. Support for the amendments and new claims can be found throughout the subject specification (for example pages 23-26) and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 10-26 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 10 and 13 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. Applicants gratefully acknowledge the Examiner's helpful suggestions concerning amendments to the claim language. In accordance with the Examiner's suggestions, Applicants have amended claim 10 to delete reference to "said insert" and replace it with "an insert." In addition, claim 13 has been amended to recite origin "of" replication. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claim 19 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action argues that the subject invention fails to adequately describe a representative number of species of the genus of truncated LacZ gene products and that, because the genus is highly variant, the description is considered insufficient. Applicants respectfully traverse.

Applicants respectfully submit that the specification provides adequate written support for the invention as currently claimed and that it is not necessary that each truncation variant of the lacZ gene be described in the specification in order to satisfy the written description requirement of section 112. For example, the full length sequence of the lacZ gene is, and has been, known in the art (see, for example, Accession Number J01636 (attached hereto) teaching the lacZ coding sequence that extends from nucleotides 1284 through 4358 (the CDS coding region is 3075 nucleotides in length [accession number AAA24053.1])). The specification teaches that any truncation variant of the lacZ gene can be used so long as the variant allows one to distinguish between colonies containing high or low vector copy numbers on the basis of color (*e.g.*, dark blue coloration versus light blue coloration; see specification, page 27). Thus, it is respectfully submitted that the subject

specification teaches that any lacZ gene product, smaller than full length, can be used in the practice of the subject invention provided that the smaller gene product confers coloration of colonies harboring vectors containing the insert (*e.g.*, dark blue coloration when expressed in high copy numbers and light blue (or white) coloration when expressed in low copy numbers). The specification further teaches genes encoding truncation variants of LacZ containing nucleotides 1-292, 1-326, or 1-392 are suitable for use in the subject invention. Indeed, the specification discloses one truncation variant of the LacZ gene in SEQ ID NO: 7 (see Sequence Listing and page 12, lines 4-14). Furthermore, plasmids containing truncated forms of LacZ are described in the subject specification (see pGenDel [SEQ ID NO: 1; Figure 1, and Example 1] and pGenBac1/pGenBac2 [Figures 13-14 and Examples 6-7]). Thus, at a minimum, the specification sets forth that polynucleotide fragments comprising at least 292 nucleotides of the lacZ gene product are useful in the practice of the claimed invention. Accordingly, it is respectfully submitted that the specification provides adequate written description of the various truncation variants useful in the practice of the subject invention and that one skilled in the art would have recognized that any lacZ coding sequence smaller than the full length lacZ coding sequence that was capable of conferring dark or light blue coloration (dependent upon the copy number of the vector) was encompassed by the claims of the subject invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 10 and 12-19 are rejected under 35 U.S.C. §112, first paragraph, as nonenabled by the subject specification. The Office Action asserts that while the subject specification is enabled for determining the presence of an insert into a vector, whereby the vector comprises a strA+ gene or comprises hybridization sites for sequencing primers to allow sequencing of the DNA insert, it is not enabled for determining a change in copy number of a vector or determining the presence of an insert into a vector comprising detecting any selectable marker, comprising detecting expression by blue color formation of any truncation of lacZ, or comprising determining the copy number of the vector.

The Office Action undertakes a Wands-type analysis of the subject application and considers the following factors: 1) the state of the prior art and the predictability or unpredictability of the art [arguing that antibiotic resistance and gene copy number in different bacterial strains is unpredictable]; 2) the amount of direction or guidance provided in the specification and the presence

or absence of working examples [arguing: 1) that the specification fails to provide adequate guidance as to methods for determining changes in copy number of a vector comprising any selectable marker, comprising the detection of blue color formation of any truncation of lacZ, or comprising determining the copy number of the vector ; and 2) that one skilled in the art would not accept on its face the examples given in the specification of the determination of inserting fragments into the vector pGenDel1 by detecting blue coloration or resistance to streptomycin; and that the specification fails to provide and particular guidance that resolves the experimental unpredictability associated with using any selection marker]; and 3) the breadth of the claims and the quantity of experimentation required [arguing that the claims are very broad and that since the specification fails to provide any particular guidance for experimental variables whereby high and low copy number is determined, undue experimentation would be required to practice the claimed invention]. Applicants respectfully traverse.

Applicants respectfully submit that the specification, as filed, enables the breadth of the presently claimed invention. As the Patent Office is aware, the quantity of experimentation can be "considerable", "tedious", "laborious", and "time-consuming" as long as the experiments are merely "routine". See *Ex parte* Jackson, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982) ("[t]he test [of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine."); *Ex parte* Erlich 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result).

In the case of the instant invention, Applicants respectfully submit that the specification teaches that vectors of the instant invention include at least one marker indicative of copy number. The marker can be: 1) a selectable marker that is sensitive to the copy number of the vector; or 2) a color based indicator that is sensitive to the copy number of vector (*e.g.*, lacZ or truncated forms thereof (see specification, page 25, starting at about line 24). The specification further teaches that the subject invention provides vectors can contain any marker that, for example, confers antibiotic sensitivity to cells that are normally antibiotic resistant when the marker is present in high copy numbers (*e.g.*, strA+) in the transformed cells (page 26, beginning at line 13). Thus, it is respectfully

submitted that the specification and claims clearly set forth conditions and functional properties of vectors that are within the scope of the present invention.

Applicants further submit that only routine experimentation is necessary to determine those markers suitable for use in the subject invention and that such experimentation can follow the protocols provided in the subject application at, for example, Example 1 or selection protocols well-known to those of ordinary skill in the fields of molecular biology. As a first example, it is respectfully submitted that one skilled in the art would have recognized that clones having low vector copy number can be selected using sensitivity to a particular antibiotic. For example, bacterial cells can be transformed with vectors of the subject invention that contain multiple selectable markers. These transformed cells can be isolated according to methods well-known in the art (*e.g.*, streaking cells out onto culture media and picking isolated colonies). These isolated bacterial clones can then be cultured and plated onto selective medium where growth on the medium is indicative of high copy number and failure to grow on the medium would be indicative of low copy number. In this example, resistance to the antibiotic would be conferred upon the bacterial clone as a function of the vector copy number (*i.e.*, high copy number conferring antibiotic resistance and low copy number conferring antibiotic sensitivity). Indeed, Olsen *et al.* clearly indicate that such a correlation is recognized to exist (see column 16, lines 40-55). While this type of experimentation may be tedious, laborious, considerable, and time-consuming, such experimentation is merely "routine" in the field of recombinant DNA technology.

Alternatively, selectable markers and/or truncation variants of lacZ are inserted into vectors provided by the subject invention and the vectors are used to transform host cells according to methods known in the art. The transformed host cells are then screened, according to methods well-known in the art, on appropriate medium to determine their phenotypic characteristics (*e.g.*, coloration [dark blue or light blue/white or sensitivity/resistance to selective agents]) that allows for the assessment of high or low vector copy number in a particular transformed cell and cells containing low vector copy numbers are selected for further isolation. As indicated in the specification at Example 1, cells containing high levels of strA+ are sensitive to streptomycin and/or have dark blue coloration and cells containing low levels of strA+ are resistant to the antibiotic and have light blue or white coloration (see pages 46-51). Again, while this type of experimentation may

be tedious, laborious, considerable, and time-consuming, such experimentation is merely "routine" in the field of recombinant DNA technology.

With respect to the issue raised in the Office Action that antibiotic resistance and gene copy number in different bacterial strains is unpredictable and that the specification fails to provide adequate teachings as to methods for determining the change of copy number in a vector comprising the use of any selectable marker, comprising the detection of blue coloration, or comprising determining the copy number of the vector, it is respectfully submitted that the vectors of the subject invention overcome these issues. For example, issues such as antibiotic sensitivity and gene copy number are controlled by the vectors of the subject invention. The copy number of the vector is controlled by virtue of the location of DNA inserts in the vectors (see, for example, specification, page 20, lines 8-24; and page 21, line 10 through to page 25, line 22). Vectors that contain inserts that confer sensitivity or resistance to a particular antibiotic when expressed in high copy number do not contain inserts in the high copy number origin of replication (which contain at least one cloning site); accordingly, copy number would be expected to be high organisms containing such vectors and the sensitivity or resistance of an organism to a particular selective agent would be a function of the vector copy number. Indeed, the citation to Olsen *et al.* provided in the Office Action clearly indicates that there is a linear correlation between the number of gene copies and antibiotic resistance (see column 16, lines 40-55). Additionally, it is respectfully submitted that methods of determining the copy number of a vector within a cell are taught in the subject application or can be accomplished according to methods known to the skilled artisan, including visual observation of the colonies for dark or light blue coloration (see, for example, page 23, last paragraph). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 10-20 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 100-107 of U.S. Patent No. 6,022,716. Applicants respectfully assert that the claims are not obvious over the cited patent. However, in the interest of expediting prosecution in this matter, a terminal disclaimer is transmitted herewith. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 20 is rejected under 35 U.S.C. § 102(b) as anticipated over Olsen (U.S. Patent No. 4,567,141). The Examiner asserts that the Olsen patent teaches a method of determining copy

number of a vector comprising a strA+ gene wherein host cells are able to grow in the presence of streptomycin when the strA+ gene is present in low copy number, but unable to grow in streptomycin when the strA gene is present in high copy numbers. Applicants respectfully assert that the Olsen patent does not anticipate the claimed invention as it fails to teach the strA+ gene or the construction of a vector containing the same. The cited portions of the patent refer to aminoglycoside modifying enzymes that confer streptomycin resistance (an adenylyltransferase and/or a phosphotransferase (column 16, lines 3-6). StrA+ is a ribosomal protein (see attached description of Accession Number J01688). Accordingly, it is respectfully submitted that the cited patent cannot anticipate the claimed invention as it fails to teach a recited element of the claimed invention, namely strA+ and reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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